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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/700,806	03/12/2002	Ben-Quan Shen	P1735R1	4225
7590	09/01/2005		EXAMINER	
DENISE M. KETRELBERGER P.O. BOX 2903 MINNEAPOLIS, MN 55402-0903			ZOLTAN JONES, ALEXANDRA	
			ART UNIT	PAPER NUMBER
			1646	

DATE MAILED: 09/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/700,806	SHEN ET AL.	
	Examiner Alexandra Zoltan-Jones, PhD	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) Responsive to communication(s) filed on 24 May 2005.  
 2a) This action is **FINAL**.                    2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) Claim(s) 1,8,10,14,16,19,23-25,27-30 and 32-42 is/are pending in the application.  
 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 1,8,10,14,16,32 and 35-42 is/are rejected.  
 7) Claim(s) 19,23-25,27-30,33,34 is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) Notice of References Cited (PTO-892)  
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)  
 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
 Paper No(s)/Mail Date 11/22/04, 5/24/05
- 4) Interview Summary (PTO-413)  
 Paper No(s)/Mail Date. \_\_\_\_\_.  
 5) Notice of Informal Patent Application (PTO-152)  
 6) Other: \_\_\_\_\_

**RESPONSE TO AMENDMENT**

Applicant's amendment filed May 24, 2005 is acknowledged. Claims 2-7, 9, 11-13, 15, 18, 20-22 and 26 were cancelled. Claims 17 and 31 were withdrawn. Claims 1, 14, 16, 19, 23, 27, 28 and 30 have been amended. Claims 32-42 are new. Claims 1, 8, 10, 14, 16, 19, 23-25, 27-30, 32- 42 are pending and under consideration. The text of those sections of Title 35 U.S. Code not included in this office action can be found in a prior office action.

***Claim Rejections Withdrawn***

Claims 1, 8, 10, 22-24, and 26-30 were rejected under 35 U.S.C. 112 first paragraph for failure to enable any person skilled in the art to make and/ or use the invention commensurate in scope with the claims. The specification does not reasonably provide enablement for a method of treating diabetes. The rejection is withdrawn in response to Applicant's removal of diabetes from the list of nitric oxide-associated disorders and the cancellation of claims 22 and 26.

Claims 1, 8, 10, 14, 15, 21, 22, 26-29 were rejected under 35 U.S.C. 112 first paragraph for failure to provide enablement for VEGF variants with one or more amino acid substitutions in a loop containing Flt-1 contact residues. Applicant's amended claims describe VEGF variants with amino acid substitutions in different binding regions, so as to modify binding affinity of VEGF to KDR and Flt-1 receptors. The rejection is withdrawn in response to applicant's amended claims and the cancellation of claims 15, 21, 22 and 26.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 16, 32, 35-42 are rejected as being unpatentable under 35 U.S.C. 103(a) over Keyt *et al.* in view of Meyer *et al.* The rejection of Claims 1, 8, 10, 14 as being unpatentable under 35 U.S.C. 103(a) over Keyt *et al.* in view of Meyer *et al.* is maintained.

Applicants argue that the Examiner has failed in the least to establish that the claimed combination of references teaches or suggests all the elements of Applicants' claims. Applicants re-assert the fact that to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of

ordinary skill in the art, to modify the reference or to combine reference teachings.

Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Applicants' arguments have been fully considered but have not been deemed persuasive.

Keyt *et al.* teach VEGF receptor agonists that exhibit selective binding affinity for KDR or Flt-1 receptors. Keyt *et al.* use charged-to-alanine scanning mutagenesis of the VEGF receptor-binding domain (1-110) to teach receptor binding determinants for KDR and Flt-1. In one such experiment, Keyt *et al.* examines the full range of VEGF<sub>110</sub> mutants in receptor binding assays to determine their affinities to KDR and Flt-1 receptors (Figure 4, p 5643). Keyt *et al.* teach that mutation in different regions of the VEGF receptor-binding domain affects the selectivity for KDR or Flt-1. The variants identified by Keyt *et al.* include those with substitutions at positions 19 and 23, as well as 63, 64, 66 or 67. Although Keyt *et al.* point out the obviously critical role of Flt-1 and KDR in growth and development of normal vascular endothelium (p 5654, column 2), they do not teach administering the variants for the treatment of hypertension, angina, thrombosis, heart failure or atherosclerosis.

Meyer *et al.* teach the use of a VEGF variant (VEGF-E) that is selective for KDR receptor, and binds VEGFR with greater affinity than wild type VEGF. Further, Meyer *et al.* propose the use of this variant in the treatment of coronary heart disease or critical limb ischemia (p 371, column1). It would have been obvious to one of skill in the art to substitute any of the VEGF mutants that are relatively selective for KDR or Flt-1, taught

by Keyt *et al.*, for VEGF-E, described by Meyer *et al.* One of skill in the art would have been motivated to do so because these mutants have shown selective binding affinity for either KDR or Flt-1 receptor, and represent tools for determining the functional significance of the KDR and Flt-1 receptors in angiogenesis and proliferation. At the time of invention, it was commonly known in the art that the angiogenic properties of VEGF were useful in the treatment of hypertension. See Van Belle *et al.* (1997), Losordo *et al.* (1998), Rosengart *et al.* (1999), Isner *et al.* (1999). Cited in previous Office Action.

Although Meyer *et al.* and Keyt *et al.* are all silent as to the effect of VEGF on the production of NO, and the length of NO production, NO is known to be an essential mediator of VEGF-induced angiogenesis. Kroll *et al.* (1998, *Biochem. Biophys. Res. Comm.* 252: 743-746) teach that VEGF induces expression of eNOS and iNOS through the KDR receptor, but has little stimulatory effect on eNOS and iNOS levels via Flt-1 signaling. Thus, during the process of treating an individual for hypertension, angina, thrombosis heart failure or atherosclerosis, manipulation of the VEGFR via VEGF variants would inherently induce changes in eNOS and iNOS expression commensurate in scope with the claims.

#### ***Claim Objections***

Claims 19, 23-25, 27-30, 33 and 34 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

#### ***Conclusion***

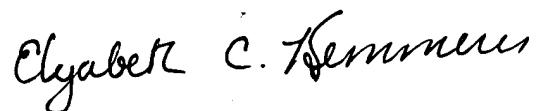
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Claims 1, 8,10, 14, 16, 35-42 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexandra Zoltan-Jones, PhD whose telephone number is (571) 272-3325. The examiner can normally be reached on Monday-Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on (571) 272-0829. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



AZJ

ELIZABETH KEMMERER  
PRIMARY EXAMINER